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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,328	02/12/2002	Jeff Steven Grotelueschen Hall	FORS-06930	5712
72960	7590	11/01/2007	EXAMINER	
Casimir Jones, S.C.			SITTON, JEHANNE SOUAYA	
440 Science Drive			ART UNIT	
Suite 203			PAPER NUMBER	
Madison, WI 53711			1634	
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			11/01/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Office Action Summary</b></p>	<p><b>Application No.</b></p> <p align="center">10/074,328</p>	<p><b>Applicant(s)</b></p> <p align="center">GROTELUESCHEN HALL ET AL.</p>	
	<p><b>Examiner</b></p> <p align="center">Jehanne S. Sitton</p>	<p><b>Art Unit</b></p> <p align="center">1634</p>	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 June 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 101, 104-106, 111-113 and 115-125 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 101, 104-106, 111-113 and 115-125 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Currently, claims 101, 104-106, 111-113 and 115-125 are pending in the instant office action. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied. They constitute the complete set being presently applied to the instant Application. This action is Non-FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejections made in the previous office action, as being anticipated by or obvious over Harrington I or Harrington II are withdrawn in view of the amendment to claim 101. The claims now require that the thermostable 5' nuclease which lacks synthetic activity function to cleave a nucleic acid cleavage structure at a temperature of at least 55 deg. C. The specification the term "cleavage structure" as "a structure which is formed by the interaction of a probe oligonucleotide and a target nucleic acid to form a duplex, said resulting structure being cleavable by a cleavage means, including but not limited to an enzyme. The cleavage structure is a substrate for specific cleavage by said cleavage means in contrast to a nucleic acid molecule which is a substrate for non-specific cleavage by agents such as phosphodiesterases which cleave nucleic acid molecules without regard to secondary structure". There is no evidence in either reference or the art in general, that the mammalian FEN-1 endonucleases taught by Harrington I and II would function at the temperatures now encompassed by the amended claims.

***Claim Rejections - 35 USC § 112***

4. Claim 113 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The preliminary amendment filed 2/12/2002 canceled claims filed with the original application and added new claims without designating where such amendments are supported by the specification. Instant claim 113 recites, "a third oligonucleotide complementary to a third region of said target nucleic acid, upstream of said first region of said target nucleic acid", however support for such amendment could not be found in the specification or the claims as originally filed. Figure 29 provides an embodiment of the invention wherein a target has 3 separate regions, with 2 oligonucleotides hybridized to such, however, the specification does not appear to provide support for a third oligonucleotide complementary to a third region of said target oligonucleotide upstream of said first region of said target. Therefore, the addition of claim 113 appears to add new matter to the claimed invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 115 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 115 recites “second target” however the term lacks sufficient antecedent basis as no “first target” nucleic acid is contained within the set of reagents of claim 101.

***Claim Rejections - 35 USC § 102***

7. Claims 101, 104-106, 111-112, 115-117, and 123-125 rejected under 35 U.S.C. 102(b) as being anticipated by Dahlberg.

With regard to claim 101, Dahlberg teaches a set of reagents that comprises a 5' nuclease lacking synthetic activity wherein the 5' nuclease functions to cleave a nucleic acid cleavage structure at a temperature of at least 55 deg C (see example 2). Dahlberg further teaches a target (claim 115, it is noted that the claims do not require that the first and second target be different, therefore more than one copy of the target nucleic acid can be considered first, second, third, etc, target nucleic acids) nucleic acid which contains a second region which is downstream and contiguous to a first region (see Fig. 16b, pilot oligonucleotide). Dahlberg teaches a first oligonucleotide containing a charged adduct (a “charged adduct” is broadly interpreted to encompass a single nucleotide or charged phosphate group; with regard to claims 124 and 125, the substrate strand comprises an uncleavable region) as well as a portion that is completely complementary to the first region (substrate strand, see Fig. 16b). Dahlberg teaches a second oligonucleotide with a 3' portion and a 5' portion, wherein the 5' portion is completely complementary to a second region of the target oligonucleotide (primer). It is noted that the claims do not require that the 5' portion be completely complementary to the entire, that is the full length of the second region.

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With regard to claim 104, Dahlberg teaches administering such oligonucleotides to a gel, which is considered a solid support.

With regard to claims 105 and 106, Dahlberg teaches a method wherein cleavage structures are subjected to cleavage reactions with 5' nucleases wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis.

With regard to claim 112, Dahlberg teaches a buffer solution (see page ).

With regard to claim 116, the claim sets forth no structural limitations for "linker". Therefore the term has been given it's broadest reasonable meaning which encompasses the sugar group of the nucleotide.

With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, the substrate molecule comprises a label at it's 5' end (claim 123).

8. Claims 118-119 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlberg in view of Urdea.

Dahlberg teaches a set of reagents that comprises a 5' nuclease lacking synthetic activity wherein the 5' nuclease functions to cleave a nucleic acid cleavage structure at a temperature of at least 55 deg C (see example 2). Dahlberg further teaches a nucleic acid which contains a second region which is downstream and contiguous to a first region (see Fig. 16b, pilot oligonucleotide). Dahlberg teaches a first oligonucleotide containing a charged adduct as well as a portion that is completely complementary to the first region (substrate strand, see Fig. 16b). Dahlberg teaches a second oligonucleotide with a 3' portion and a 5' portion, wherein the 5'

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portion is completely complementary to a second region of the target oligonucleotide (primer). It is noted that the claims do not require that the 5' portion be completely complementary to the entire, that is the full length of the second region. With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, the substrate molecule comprises a <sup>32</sup>P label at its 5' end.

Dahlberg does not teach wherein the first oligonucleotide comprising a charged adduct comprises a detectable molecule which is fluorescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and 3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Dahlberg with fluorescein on an amino modified base, as taught by Urdea because Urdea teaches detection of cleaved nucleic acids and teaches labels such as fluorescein on an amino modified base can be used. The ordinary artisan would have been motivated to improve the method of Dahlberg with the use of the labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactively labels.

9. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlberg in view of Corey.

Dahlberg teaches a set of reagents that comprises a 5' nuclease lacking synthetic activity wherein the 5' nuclease functions to cleave a nucleic acid cleavage structure at a temperature of at least 55 deg C (see example 2). Dahlberg further teaches a nucleic acid which contains a second region which is downstream and contiguous to a first region (see Fig. 16b, pilot oligonucleotide). Dahlberg teaches a first oligonucleotide containing a charged adduct as well as a portion that is completely complementary to the first region (substrate strand, see Fig. 16b). Dahlberg teaches a second oligonucleotide with a 3' portion and a 5' portion, wherein the 5' portion is completely complementary to a second region of the target oligonucleotide (primer). It is noted that the claims do not require that the 5' portion be completely complementary to the entire, that is the full length of the second region. Dahlberg does not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased  $K_a$  by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the assays of Dahlberg with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Dahlberg, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Dahlberg for the purpose of accelerating hybridization, as taught by Corey, in the assays of Dahlberg, and thus enhancing the assays of Dahlberg.

### ***Double Patenting***

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 101, 104-106, 111-113, 115-120 and 122-125 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/031,487. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and its 3' portion does not. As defined by the specification of the '487 application, the 2<sup>nd</sup> oligonucleotide

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hybridizes to the target downstream of the first oligonucleotide, and a kit comprising “an invasive cleavage detection assay” encompasses a thermostable 5’ nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the ‘487 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/031,487 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5’ nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3’ portion and a 5’ portion wherein the 5’ portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-7 of the ‘487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5’ portion and a 3’ portion which hybridizes to the 5’ UTR of HCV (target) and a second oligonucleotide which comprises a 5’ portion and a 3’ portion wherein the 5’ portion hybridizes

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to the HCV 5' UTR and it's 3' portion does not. As defined by the specification of the '487 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '487 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '487 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '487 application.

This is a provisional obviousness-type double patenting rejection.

13. Claims 101, 104-106, 111-113, 115-120, and 122-125 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the

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first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '408 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to a target

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nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to a second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2<sup>nd</sup> oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1<sup>st</sup> or 2<sup>nd</sup> oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '408 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '408 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '408 application

This is a provisional obviousness-type double patenting rejection.

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15. The response provides no arguments with regard to the obviousness type double patenting rejections set forth above. Accordingly, the rejections are maintained for the reasons made of record above and in previous office actions.

### *Conclusion*

16. No claims are allowable over the cited prior art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/  
Primary Examiner  
Art Unit 1634  
10/26/2007